

## Compared With Whom?

### Addressing the Prognostic Value of Ambulatory Blood Pressure Categories

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*Two statisticians meet.*

*How do you do?*

*How do I do? Compared to whom?*

—Anonymous

In several longitudinal studies in the general population<sup>1–4</sup> and referred cohorts of hypertensive patients,<sup>5,6</sup> ambulatory blood pressure (BP) proved superior to clinic BP for prediction of the risk of major cardiovascular events and mortality. These studies analyzed ambulatory BP as a continuous variable.<sup>1–6</sup> However, for risk stratification and management of patients, clinicians need operational thresholds, which, by definition, are somewhat arbitrary.

Indeed, several clinical categories based on ambulatory BP have been proposed over the last 2 decades well before the evidence of the prognostic superiority of ambulatory over clinic BP as continuous variables became clear. “White-coat” hypertension (WCH), “masked” hypertension, “nondipping,” “overdipping,” and “early morning rise” BP patterns are examples of clinical categories of which the prognostic value has been investigated in outcome-based studies.

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When addressing the prognostic value of a given clinical category, it is crucial that the reference group be clearly defined. Albeit apparently obvious, the conclusion that a given category is a condition of “increased,” “unchanged,” or “decreased” risk must require a precise and clinically applicable definition of the control group.

For example, the prognostic impact of WCH, broadly defined by the coexistence of elevated clinic BP with a normal ambulatory BP, has been addressed in some outcome-based studies. The majority of these studies<sup>7</sup> examined cohorts of referred hypertensive subjects and compared the group with WCH either with subjects with higher ambulatory BP (ambulatory or sustained hypertension) or with healthy normotensive subjects, taken as a reference group.

Importantly, in most of these studies, no attempts were made to further subdivide the normotensive subjects into those with normal and those with elevated ambulatory BP. The underlying reason seems quite obvious: if ambulatory BP is intended as a diagnostic tool to improve risk stratification in clinically hypertensive subjects, the “no-added-risk” group should include the totality of clinically normotensive subjects for whom there is universal evidence that clinic BP is a fundamental determinant of outcome.

By contrast, if ambulatory BP is intended as a potential tool to improve risk stratification in the general population, the attempt to divide those with normal from those with elevated ambulatory BP in the normotensive group becomes justified. There is growing evidence that clinically normotensive subjects with elevated ambulatory BP (masked hypertension) have greater organ damage and a higher incidence of cardiovascular events than those with normal ambulatory BP.<sup>8</sup> This supports the practice of subclassifying the clinically normotensive subjects on the basis of their level of ambulatory BP. For the time being, it seems reasonable to speculate that any implication regarding the clinical use of ambulatory BP as coming out from general population studies with stratification of clinically normotensive by ambulatory BP categories remains applicable to the general population, not necessarily to referred cohorts of subjects with clinical hypertension.

Consistent with this line of thinking should be the interpretation of a report from the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) Study published in this issue of *Hypertension*.<sup>9</sup> This article is an extension of a previous report from the PAMELA Study, which addressed the prognostic impact of clinic and ambulatory BP as continuous variables. Here, the authors made multiple comparisons of subjects with normal and abnormal values defined by clinic BP, 24-hour ambulatory BP, and self-measured home BP. Cardiovascular and all-cause mortality were the outcome measures. Similarly to other general population studies, the clinically normotensive subjects with elevated 24-hour ambulatory BP or home BP were not included in the normotensive (reference) group, but in the distinct category of masked hypertension. Notably, prevalence of these subjects in the total population was ≈15%.

Although only summary percentages, not actual numbers, of cardiovascular events were provided, and although the hazard ratios (HRs) for cardiovascular events in the different ambulatory BP categories were not reported as actual numbers but only displayed graphically, the most remarkable finding of this report was the increased risk of cardiovascular mortality in the 2 groups with WCH and masked hypertension as compared with the normotensive reference group, regard-

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less of whether the diagnoses of WCH and masked hypertension were based on 24-hour ambulatory or self-measured BP.

Different results have been obtained by Ohkubo et al<sup>10</sup> in a general population study from Japan and by Fagard et al<sup>11</sup> in a general practice in Belgium. In the study from Japan,<sup>10</sup> the risk of cardiovascular mortality did not differ between the normotensive control group, from which the subjects with masked hypertension had been excluded, and the group with WCH (HR, 1.54; 95% confidence interval [CI], 0.73 to 3.21). Also, the risk of stroke (HR, 1.07; 95% CI, 0.58 to 2.07) and that of cardiovascular mortality and stroke combined (HR, 1.28; 95% CI, 0.76 to 2.14) did not differ between the normotensive control group and the group with WCH. When compared with the normotensive subjects, those with masked hypertension showed an increased risk of stroke (HR, 2.17; 95% CI, 1.31 to 3.60) but not of cardiovascular mortality (HR, 1.88; 95% CI, 0.95 to 3.72). In the study from Belgium,<sup>11</sup> the risk of cardiovascular events was not dissimilar in the normotensive control group, the group with WCH, and that with masked hypertension. An excess risk of events was noted only in the subset with ambulatory (sustained) hypertension.

Further studies should clarify the clinical value of ambulatory and home BP in the general population. An important caveat to consider, however, is that the exclusion of subjects with masked hypertension from the normotensive control group may be expected to produce some reduction in the overall level of risk in this selected group. Consequently, caution is needed when comparing the results of population studies from those obtained in hypertensive patients in which the normotensive control group has been analyzed as a whole, with inclusion of the subjects with masked hypertension.

### Conclusions

Context and interpretation of clinical research focused on the potential value of 24-hour ambulatory BP and home BP for identification of masked hypertension in clinically normotensive subjects should be maintained distinct from that aimed at clarifying the clinical place of 24-hour ambulatory BP and home BP in subjects with traditional diagnosis of hypertension. How to make the best use of BP categories defined by

ambulatory and home BP in subjects with clinical hypertension is still a topic for discussion and research. At present, it seems reasonable to suggest that any "normotensive control group" included in this kind of research should include the totality of clinically normotensive subjects. By contrast, the growing research area regarding masked hypertension may greatly benefit from general population studies and even studies in 100% clinically normotensive populations.

### References

1. Ohkubo T, Imai Y, Tsuji I, Nagai K, Watanabe N, Minami N, Itoh O, Bando T, Sakuma M, Fukao A, Satoh H, Hisamichi S, Abe K. Prediction of mortality by ambulatory blood pressure monitoring versus screening blood pressure measurements: a pilot study in Ohasama. *J Hypertens*. 1997;15:357–364.
2. Hansen TW, Jeppesen J, Rasmussen S, Ibsen H, Torp-Pedersen C. Ambulatory blood pressure and mortality: a population-based study. *Hypertension*. 2005;45:499–504.
3. Sega R, Facchetti R, Bombelli M, Cesana G, Corrao G, Grassi G, Mancia G. Prognostic value of ambulatory and home blood pressures compared with office blood pressure in the general population: follow-up results from the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study. *Circulation*. 2005;111:1777–1783.
4. Dolan E, Stanton A, Thijs L, Hinedi K, Atkins N, McClory S, Den Hond E, McCormack P, Staessen JA, O'Brien E. Superiority of ambulatory over clinic blood pressure measurement in predicting mortality: the Dublin outcome study. *Hypertension*. 2005;46:156–161.
5. Perloff D, Sokolow M, Cowan R. The prognostic value of ambulatory blood pressure. *JAMA*. 1983;249:2792–2798.
6. Staessen JA, Thijs L, Fagard R, O'Brien ET, Clement D, de Leeuw PW, Mancia G, Nachev C, Palatini P, Parati G, Tuomilehto J, Webster J. Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension. Systolic Hypertension in Europe Trial Investigators. *JAMA*. 1999;282:539–546.
7. Verdecchia P. Prognostic value of ambulatory blood pressure: current evidence and clinical implications. *Hypertension*. 2000;35:844–851.
8. Pickering TG, Davidson K, Gerin W, Schwartz JE. Masked hypertension. *Hypertension*. 2002;40:795–796.
9. Mancia G, Facchetti R, Bombelli M, Grassi G, Sega R. Long-term risk of mortality associated with selective and combined elevation in office, home, and ambulatory blood pressure. *Hypertension*. 2006;47:846–853.
10. Ohkubo T, Kikuya M, Metoki H, Asayama K, Obara T, Hashimoto J, Totsune K, Hoshi H, Satoh H, Imai Y. Prognosis of "masked" hypertension and "white-coat" hypertension detected by 24-h ambulatory blood pressure monitoring 10-year follow-up from the Ohasama study. *J Am Coll Cardiol*. 2005;46:508–515.
11. Fagard RH, Van Den Broeke C, De Cort P. Prognostic significance of blood pressure measured in the office, at home and during ambulatory monitoring in older patients in general practice. *J Hum Hypertens*. 2005;19:801–807.